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The oxytocin receptor gene *OXTR* is not associated with face recognition.

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Abstract

Individual differences in face recognition have been linked to a single-nucleotide polymorphism (rs237887) of *OXTR*, the gene that encodes the oxytocin receptor (Skuse et al., 2014). In that study, participants were assessed by Warrington's test of Face Recognition, but performance on Warrington's test has been shown not to rely purely on face recognition processes. We administered the widely used Cambridge Face Memory Test—a purer test of face recognition—to 370 participants. Performance was not significantly associated with rs237887, or with 16 other SNPs of *OXTR* that we genotyped, or with a further 75 imputed SNPs. We also administered three other tests of face processing (Mooney Face Test, Glasgow Face Matching Test, and Composite Face Test), but performance was never significantly associated with rs237887, or with any of the other genotyped or imputed SNPs, after corrections for multiple testing. Additionally, we found no associations between *OXTR* and autism-spectrum quotient (AQ).

Keywords

OXTR; oxytocin-receptor gene; rs237887; Cambridge Face Memory Test; face recognition; AQ

Introduction

Polymorphisms of the oxytocin receptor gene *OXTR* have been linked to individual variations in an array of human social behaviours, including maternal sensitivity, empathy, pro-social behaviour and recognition of affect (Ebstein et al., 2012; Feldman et al., 2016; Kogan et al., 2011; Poulin et al., 2012). Genetic variations in *OXTR* have also been linked to autism spectrum disorder (Di Napoli et al., 2014; LoParo & Waldman, 2015). However, although *OXTR* has been a favourite candidate gene for social behaviours, the evidence is not consistent (Cornelis et al., 2012; Kiy et al., 2013). Thus a recent meta-analysis of two commonly cited single-nucleotide polymorphisms (SNPs) of *OXTR* (rs53576 and rs2254298) found that the average effect size did not differ from zero for either empathetic aspects of personality or for social behaviours (Bakermans-Kranenburg & van IJzendoorn, 2014). And an analysis of *OXTR* polymorphisms in a large sample found no overall association with a measure of social integration based on marital status, contact with close friends and participation in community groups (Chang et al., 2014).

A recent paper added face recognition to the list of behaviours positively associated with *OXTR*: Skuse et al. (2014) report a significant association between performance on the Warrington Test of Recognition Memory for Faces and the single nucleotide polymorphism (SNP) rs237887, which lies in the third and last intron of the oxytocin receptor gene. The subjects were a subset ($N = 333$) of a sample of high-functioning children with autism and their first-degree relatives (their parents and siblings). From the eighteen SNPs of the *OXTR* gene that Skuse et al. (2014) genotyped, rs237887 was the only one to be found significantly associated with performance on the Warrington test. This effect was mostly driven by the “neurotypical” first-degree relatives, despite the focus in the study being on children with autism. Skuse and colleagues genotyped an

additional 42 SNPs from the region surrounding this gene, but none of these SNPs were significantly associated with performance on the Warrington test of face recognition (Skuse et al., 2014).

However, the validity of the Warrington Test as a pure index of face recognition ability has previously been questioned: Duchaine and Weidenfeld (2003) observed that some participants could perform normally on this test even when the internal features of the face stimuli had been removed. Duchaine and Nakayama (2006) went on to develop the Cambridge Face Memory Test (CFMT), which, since its development, has been used in a wide range of studies, investigating both prosopagnosics and normals (e.g. Busigny et al., 2010; Germine et al., 2012; Hedley et al., 2011; Wilmer et al., 2010).

In the course of a genome-wide association study (GWAS), we genotyped 17 SNPs of the *OXTR* gene, and we investigated another 75 SNPs of *OXTR* using imputation methods. We used four different tests of face perception and recognition, in order to index several aspects of face processing: The Cambridge Face Memory Test (mentioned above), the Mooney Face test, the Glasgow Face Matching Test, and the Composite Face test. In addition, we measured the autism-spectrum quotient (AQ).

The *Cambridge Face Memory Test* (CFMT) has been administered to thousands of participants, in both online studies and lab-based studies (Germine et al., 2012; Wilmer et al., 2014). Performance on the CFMT is highly heritable, as shown by a twin study (Wilmer et al., 2010), and performance has little or no correlation with general intelligence (Shakeshaft & Plomin, 2015; Wilmer et al., 2014). Bate et al. (2014) report a significant increase of CFMT performance after intranasal administration of oxytocin, though for prosopagnosics only; a similar pattern was found for a face-matching test (the

Cambridge Face Perception Test).

The original *Mooney Face Test* is a test of face perception that has been widely used in clinical testing. It comprises forty images that each depict a face. The images consist solely of pure black and pure white elements, without any shading (Mooney, 1957). This renders the perception of the faces all or none: Either the black and white elements coalesce meaningfully into a face, or they remain seemingly unrelated. In the present study we used an online, three-alternative forced-choice version of the test, incorporating the original forty images (Verhallen et al., 2014).

The *Glasgow Face Matching Test* (GFMT) is a test of face matching, in which the participant is shown two photographs simultaneously that depict either the same person or two different persons (Burton et al., 2010). For a given pair of photographs of a particular person, the two images were obtained using different cameras, different angles and different lighting; hence photographs depicting the same person are not physically identical. This test shows strong correlations with tests of face recognition (Burton et al., 2010).

The *Composite Face Test* sequentially presents two faces, each of which is composed of a top half and a bottom half originating from two different faces (Richler et al., 2011; Young et al., 1987). On a given trial, the top half of the second face may or may not be the same as the top half of the first face. Similarly, the bottom halves might or might not differ. The participant is asked, for the top half only, whether it remained the same from one face to the next, or not. Changes in the bottom half are thought to interfere with participants' judgment of the top half when the two halves are aligned to form one face; when the two halves are misaligned, participants experience no interference. This

difference in performance is thought to reflect *holistic processing* (Rossion, 2013; Richler & Gauthier, 2013), a measure that has been found to correlate with face recognition (Richler et al., 2011).

Materials & Methods

Participants. For analyses with the four tests of face processing, our sample consisted of 370 participants (235 female ; see Verhallen et al., 2016 for more detailed descriptive statistics of the four tests), while for analyses with the AQ questionnaire (Baron-Cohen et al., 2001) our sample consisted of 521 participants (333 female). Both samples are subsets of a cohort of 1,060 participants who had previously completed a battery of perceptual tests in our laboratory as part of the PERGENIC project (Bosten et al., 2015; Goodbourn et al., 2014; Lawrance-Owen et al., 2013). Ethical permission for the study was given by the Cambridge University Psychology Research Ethics Committee. Our participants were healthy young adults between the ages of 18 and 42 ($M = 24$ years), all Caucasian. The majority were students at the University of Cambridge.

Materials. The Mooney test we used is described in Verhallen et al. (2014): it employed the forty original Mooney faces (Mooney, 1957) in an online three-alternative forced-choice paradigm. We used the shortened Glasgow Face Matching Test as described in Burton et al. (2010), and the Cambridge Face Memory Test as described in Duchaine and Nakayama (2006). The Composite Face Test we used is the version developed by Richler and colleagues (2011) incorporating stimuli from the Max Planck Institute Face Database (Troje & Bühlhoff, 1996) and following the complete design; we administered this test according to the procedure described by Richler et al. (2011). Two performance variables were investigated for this test: the *holistic index* – calculated by regressing participants' performance on the misaligned congruent trials from their performance on the aligned congruent trials (see Verhallen et al., *under review*) – and a more straightforward percentage correct across all trials (referred to in this paper as 'raw score').

Procedure. The performance data were collected online. All participants completed the four tests of face processing in the same sequence: first the Mooney test, then the GFMT, the CFMT, and finally the Composite test. The procedure for the Mooney test is described in Verhallen et al. (2014); the GFMT, the CFMT, and the Composite test all were administered according to their original procedures as described in their respective sources. Since the distribution of scores is non-normal for all four tests, we converted raw performance scores to ranks; in the case that two or more participants had the same score, they were all assigned the average rank of that score. Full details of the four tests, their intercorrelations and their phenotypic correlates are given in Verhallen et al. 2016 (manuscript under review).

The fifty questions comprising the autism-spectrum quotient questionnaire (Baron-Cohen et al., 2001) were the first items in a follow-up questionnaire that previously had been administered online.

Genetics. Genetic data were collected during the original PERGENIC project. All genetic analyses were performed in PLINK (Purcell et al., 2007); imputation was performed using IMPUTE2 (Howie et al, 2009, 2011) and the 1000 genomes phased haplotypes (1000 Genomes Project Consortium, 2010). In all genetic analyses reported here, sex was entered as a covariate, as well as the top three principal components of genetic variation to control for population stratification. See Lawrance-Owen et al. (2013) and Goodbourn et al. (2014) for details on the genotyping and quality control.

Results

Performance on the Cambridge Face Memory Test ranged from 26 to 72 trials correct ($M = 54.15$, $SD = 9.04$). If we take the data from Duchaine & Nakayama (2006) as norms, the range of performance we observed is very wide: z -scores ranged from -4.04 to $+1.78$, with mean performance corresponding to a z -score of $-.47$.

Our genetic analysis of 370 healthy Caucasian participants (235 females) did not reveal a significant association between performance on the Cambridge Face Memory Test and SNP rs237887 – the SNP located in the *OXTR* gene for which Skuse et al. (2014) found a significant association. The uncorrected p -value was .88 ($r^2 = 5.89 \times 10^{-5}$) when we entered CFMT performance as ranked data (and .90 when we entered the raw performance data, where $r^2 = 4.47 \times 10^{-5}$). For the single variant rs237887, we had over 99% power to detect an association (at $\alpha = .05$) if the polymorphism accounted for 10% of phenotypic variance as estimated by Skuse et al. (2014); even a polymorphism accounting for only 2% of variance would have been detected with 86% power. The minor allele frequency (MAF) of rs237887 was .42 in our sample, which is similar to the MAF of .45 in the sample of Skuse and colleagues.

For the sixteen other SNPs within the *OXTR* gene that we genotyped, our uncorrected p -values for ranked CFMT performance ranged from .06 to .98 (see Table 1, second column) while r^2 ranged from .0098 to 1.70×10^{-6} . Sex was entered as a covariate in all genetic analyses that are presented in this paper. However, even performing the genetic analyses of ranked CFMT performance data for females and males separately did not yield a significant association with rs237887 ($p = .30$ with $r^2 = .0047$, and $p = .27$ with $r^2 = .0095$, respectively), nor with any of the other genotyped SNPs.

To further investigate *OXTR*, we imputed a 60 Kb region centred on the gene. This procedure yielded an additional 75 SNPs within the *OXTR* gene. However, among these imputed SNPs, the lowest uncorrected p -value for an association with performance on the CFMT was only .03 (see Figure 1) and no association remained significant after correction for multiple testing.

In addition to the CFMT, we administered three more tests of face processing: the Mooney test ($M = 34.9$, $SD = 2.8$, range 25–39), the Glasgow Face Matching Test ($M = 31.5$, $SD = 4.6$, range 14–40), and the Composite Face Test ($M = 137.8$, $SD = 11.6$, range 79–157). We again investigated the influence of rs237887 on performance for each of these tests, but again no association was significant (r^2 did not exceed .00029).

However, when we used ranked raw score on the Composite test, as opposed to the usual performance variable called the ‘holistic index,’ we did observe an association with rs237887: the uncorrected p -value was .04 (see Table 1, sixth column), but the association would have explained only 1.14% of variance, an effect size that is much smaller than observed by Skuse et al. (2014) for the Warrington test. Furthermore, the association would not survive a Bonferroni correction for the number of measures we investigated, and the direction of the association was in fact the opposite of that observed by Skuse et al. (2014): in our sample, participants who were homozygous for the major allele A performed better on average.

None of the other genotyped SNPs were significantly associated with performance on any of the three tests, or with ranked raw score on the Composite test, when we corrected for the seventeen genotyped SNPs (see Table 1). Nor were there significant associations with any of the 75 imputed SNPs. The genotyped SNP rs2324728 comes closest to a significant association with performance on the Mooney test. The association

is not significant if a Bonferroni correction is applied for 17 SNPs (and *a fortiori* would not be significant if we applied a Bonferroni correction for the 17 x 6 entries in Table 1); but the association approaches significance when genetic linkage between SNPs is taken into account in applying the correction for multiple testing (Li et al., 2012; see note ‘1’ to Table 1). If any polymorphism of *OXTR* were associated with face recognition, it would be more likely to be this one than rs237887.

TABLE 1

The uncorrected *p*-values for the genetic associations of seventeen genotyped SNPs within the *OXTR* gene, with performance on our four tests of face processing – CFMT, Mooney test, GFMT, Composite test *holistic index* (‘Holistic’) and Composite test raw scores (‘Comp. raw’), respectively – as well as with autism-spectrum quotient (AQ).

SNP	CFMT	Mooney	GFMT	Holistic	Comp. raw	AQ
rs2324728	.06	¹ .004	.28	.03	.12	.79
rs237884	.07	.01	.50	.05	.30	.60
rs1042778	.82	.68	.97	.56	.82	.80
rs237885	.38	.75	.20	.83	.20	.17
rs11706648	.58	.82	.43	.99	.27	.59
rs237887	.88	.85	.75	.64	.04	.59
rs2268490	.46	.88	.96	.24	.14	.82
rs237888	.35	.49	.08	.18	.03	.47
rs918316	.25	.48	.96	.78	.97	.62
rs4686301	.59	.91	.53	.57	.09	.44
rs2268491	.46	.88	.96	.44	.15	.82
rs237889	.36	.76	.41	.43	.68	.83
rs11131149	.65	.51	.65	.80	.21	.75
rs2268495	.14	.80	.03	.60	.99	.81
rs237897	.35	.54	.29	.38	.90	.31

TABLE 1

The uncorrected p -values for the genetic associations of seventeen genotyped SNPs within the *OXTR* gene, with performance on our four tests of face processing – CFMT, Mooney test, GFMT, Composite test *holistic index* (“Holistic”) and Composite test raw scores (“Comp. raw”), respectively – as well as with autism-spectrum quotient (AQ).

SNP	CFMT	Mooney	GFMT	Holistic	Comp. raw	AQ
rs237899	.98	.60	.31	.84	.86	.45
rs2301261	.61	.84	.95	.77	.08	.81

Note: For all measures except the Composite test’s holistic index, and except for AQ, performance data were entered into the analysis as ranks, whereby ties were assigned the average rank of those ties. All SNPs listed had a minor allele frequency of .05 or greater in our sample. The p -values for the SNP rs237887, for which Skuse et al. (2014) had found a significant association with face recognition (see main text), are printed in bold.

¹ *This association, between rs2324728 and ranked performance on the Mooney test, gave the lowest uncorrected p -value of all associations with the 17 genotyped SNPs of the *OXTR* gene. It would not survive a conventional Bonferroni correction ($.004 \times 17$ SNPs = .068) or even a more moderate correction that takes genetic linkage into account ($.004 \times 13.19$ ‘effective corrections’ = .053; the number of effective corrections is determined using the Genetic Type 1 Error Calculator (Li et al., 2012)).*

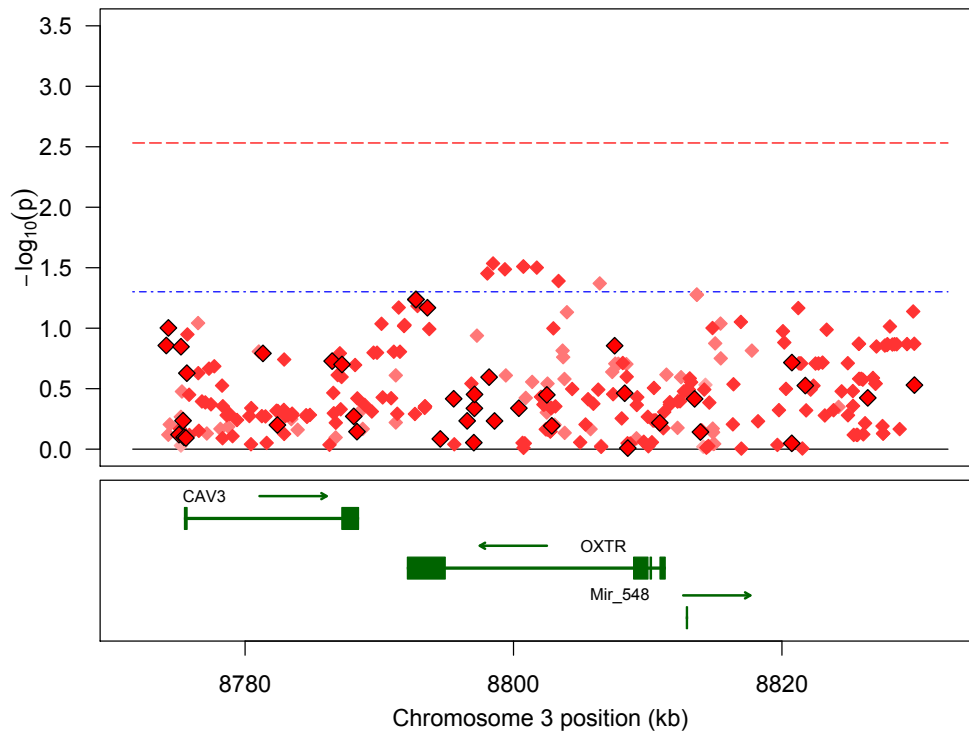


Figure 1. Regional Manbattan plot for CFMT performance, centred on the OXTR gene. Each red diamond represents a SNP: Those with black borders were genotyped (see also Table 1, second column); those without black borders were imputed (their saturation corresponds to their imputation quality). Log probability values are plotted on the y-axis; the blue dot-dash line indicates $p = .05$, while the red dashed line represents $p = .0029$ – the Bonferroni-corrected cut-off value when correcting for the seventeen genotyped SNPs. The genetic position, along chromosome three, is plotted on the x-axis. The bottom panel shows the genes in this region. The minor allele frequency was .05 or greater for all plotted SNPs.

One SNP of OXTR that repeatedly has been identified with pro-social behaviours is rs53576 (Ebstein et al., 2012; Bakermans-Kranenburg & van IJzendoorn, 2014; Kogan et al., 2011). This SNP was one of the 75 imputed SNPs that we tested, and its imputation quality was high (RSQR = .84). However, it was not significantly associated with any of our measures of face processing. For the association with performance on the CFMT in particular, the uncorrected p -value was .32.

The association between OXTR and face recognition observed by Skuse and colleagues was largely driven by the parents and siblings in their sample, none of whom “had

significant autistic traits [as measured by the autism-spectrum quotient (AQ) questionnaire], thus all could be considered neurotypical in that respect” (Skuse et al., 2014). We can confirm that our sample too was neurotypical in this respect. Of the participants who completed our tests of face processing, 316 (203 female) had also earlier completed the AQ questionnaire (Baron-Cohen et al., 2001): Their mean score was 17.85 (SD = 7.94), with a range from 3 to 39 (the maximum possible score is 50); a score of 32 or higher is suggestive of autism spectrum disorder (only 21 participants here reached this score).

There are several reports of an association between *OXTR* and autism spectrum disorder (Di Napoli et al., 2014; LoParo & Waldman, 2015). For the present population of young adults, we did therefore check whether there was a link between Autism-spectrum Quotient and polymorphisms in *OXTR*. For this analysis, we could use all 521 (333 female) participants who had served in the original cohort and who had completed the AQ questionnaire (AQ: $M = 17.32$, $SD = 7.58$, range 3–39; 25 participants scored at or above 32). As with all other genetic analyses in this paper, we entered sex as a covariate, especially since we observed a significant sex difference in AQ (Mann–Whitney $U = 25,252$, $p = .00024$; $\mu_{\text{Female}} = 16.48$, $\mu_{\text{Male}} = 18.82$). We found no significant association between AQ and rs237887 or any other genotyped SNPs (see Table 1, last column; the lowest uncorrected p -value was .17). None of the imputed SNPs, including rs53576, were significantly associated with AQ either (see Figure 2; the lowest uncorrected p -value was .07). Even when we followed Rhodes et al. (2013) in calculating a *total* AQ score—i.e. totaling the raw scores of all items, rather than labeling responses to items in a binary fashion, which is the usual approach—we observed no significant associations (uncorrected p -values ranged from .43 to .99). For genetic correlates of AQ, we had 99% power (at $\alpha = .05$) to detect associations with an effect size as small as (or greater than) r^2

= .05 (and 74% power for $r^2 > .01$; 49% power for $r^2 > .005$). Any association of *OXTR* with autism spectrum disorder may be confined to those who explicitly exhibit the condition.

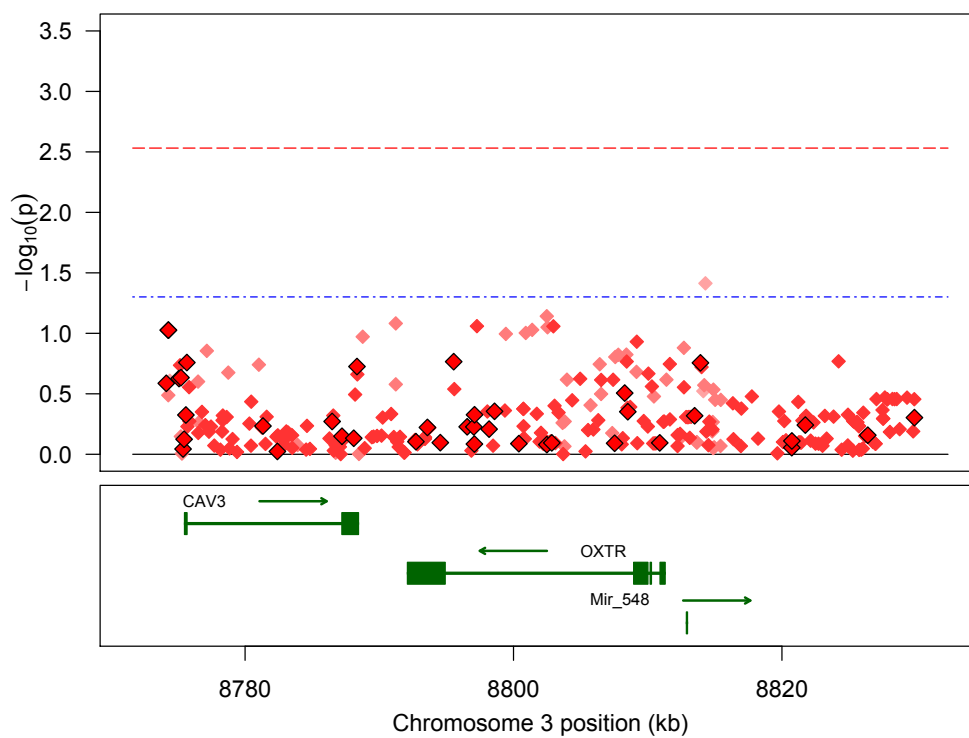


Figure 2. Regional Manhattan plot for *AQ*, centred on the *OXTR* gene. Each red diamond represents a SNP: Those with black borders were genotyped (see also Table 1, rightmost column), those without black borders were imputed (their saturation corresponds to their imputation quality). Log probability values are plotted on the y-axis; the blue dot-dash line indicates $p = .05$, while the red dashed line represents $p = .0029$ – the Bonferroni-corrected cut-off value when correcting for the seventeen genotyped SNPs. The genetic position, along chromosome three, is plotted on the x-axis. The bottom panel shows the genes in this region. The minor allele frequency was .05 or greater for all plotted SNPs.

Discussion

Our primary findings are at odds with those of Skuse et al. (2014), who reported a significant association of rs237887 with recognition memory for faces. Despite our large sample size ($N = 370$) and ample statistical power, we observed no association between rs237887 and the Cambridge Face Memory Test, which is widely accepted as a pure measure of face recognition ability. Nor did we find an association of rs237887 with the Mooney Face Test or the Glasgow Face Matching Test. A marginal association between rs237887 and raw score on the Composite Face Test was not significant after correction for multiple testing.

What then might be the critical difference between our study and that of Skuse et al. (2014)? Could it be the difference in population? Skuse et al. (2014) investigated children with autism as well as the parents and siblings of these children. However, the association they observed with rs237887 was weakest for the autistic probands, while being stronger for the parents and siblings; the association became significant (after Bonferroni correction) only for the combined sample, two-thirds of which comprised nominally healthy participants. Skuse et al. (2014) mention that they specifically selected a sample of autistic probands and their immediate family members “to maximize the range of social cognitive abilities under investigation.” Although we did not ourselves select a restricted sample, our results show a very wide range of face recognition ability (see Results). However, it remains possible that rs237887 is associated with face recognition within the special population – of relatives of children with autism – that was studied by Skuse and his colleagues (2014).

The fact that we tested our participants online instead of in the lab should not have substantially influenced the reliability of our results: Germine et al. (2012) found that

online testing ($N = 4,080$) yielded high quality data that were as reliable as data gathered from three lab-based samples (combined $N = 327$). At the request of a reviewer, we re-ran our genetic association omitting the 10 out of 370 (2.7%) participants who scored 2 or more standard deviations below the mean score on the Cambridge Face Memory Test: The results were little changed. As for a possible difference in age range of our sample as compared to that of Skuse et al. (2014), it is not possible to make a comparison, since only a subset of their total sample completed the Warrington test, and the age range for this subset is not reported.

What is possible is that the variance accounted for by rs237887 in the study of Skuse and colleagues (2014) is not variance specific to face recognition, but rather reflects some other ability required for performance on the Warrington test. One candidate might be general intelligence, since Skuse et al. (2014) observed a significant association between performance on the Warrington test and IQ ($r = .30$), whereas in contrast the CFMT exhibits little or no correlation with general intelligence (Davis et al., 2011; Shakeshaft & Plomin, 2015; Wilmer et al., 2014). Additionally, Skuse et al. (2014) do not use the raw performance data from the Warrington test, but first standardise the performance for age. Oddly, they use performance data from a test of *affect* recognition (the Ekman–Friesen test) to do so. It is unclear to what extent their observed association of *OXTR* with face recognition might be the effect of this unconventional standardisation method. When we ourselves repeated our genetic analysis using age as a covariate, the uncorrected p -values for rs237887 were little changed from those in Table 1.

Our negative finding for rs237887 is limited, of course, to the recognition of facial identity. It may well be the case that polymorphisms of *OXTR* are associated with individual differences in the ability to infer emotional states from facial expressions –

individual differences that may derive from, or contribute to, prosocial behaviours and to social anxieties.

In sum, the conclusion of Skuse et al. (2014) may still apply to a particular test, or to a particular population of relatives of children with autism, and it remains possible that polymorphisms of *OXTR* are related to individual differences in empathy or social anxiety; but what we can firmly conclude is that in a population of normal young adults there is no strong association between SNP rs237887 of the oxytocin receptor gene and the ability to recognise previously seen faces. This is the conclusion that we emphasise.

Author's contribution

All authors developed the study concept. All authors contributed to the study design. Testing and data collection were performed by all authors. RJ Verhallen performed the data analysis and interpretation under the supervision of JD Mollon. RJ Verhallen drafted the manuscript, and JM Bosten, PT Goodbourn and JD Mollon provided critical revisions. All authors approved the final version of the manuscript for submission.

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